objected to because of the following formalities: claim 15 recites "inhbiting", a mis-spelling of "inhibiting". The Examiner stated that appropriate correction is required.

In response, applicants have hereinabove amended claim 15 such that the term "inhibiting" is spelled correctly. Applicants contend that this amendment obviates the Examiner's above objection, rendering it moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the objection.

Rejection Under 35 U.S.C. §112 Second Paragraph

The Examiner rejected claims 15-16, 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in Paper No(s). 10.

Rejection of claim 15 concerning the term "defect"

The Examiner stated that claim 15 recites "defect". The Examiner stated suggested looking at the rejection in Paper No(s) 10, which applicant has not traversed.

In paper no. 10, the Examiner stated that the recitation of "defect" is vague and indefinite because it is not known what is encompassed by the term. The Examiner stated that for example, "defect" could refer to memory loss, the inability to create a memory, incomplete or incorrect memory building, or other.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point the Examiner's attention to page 15, lines 1-4 of the originally filed specification which states:

> The long term memory defect may include age-related memory loss, Alzheimer's Disease, amnesia, ischemia, shock, head trauma, neuronal injury, neuronal

toxicity, neuronal degradation, Parkinson's disease, or senility.

Accordingly, applicants contend that the specification adequately defines the term "defect" such that it is not vague and indefinite. The specification provides several examples and one skilled in the art would understand the defects associated with these examples.

Additionally, applicants contend that the specific cause of the defect is not pertinent to the claim. Applicants contend that no matter what the cause is of the defect, it is still a memory defect. Applicants respectfully believe that the Examiner is construing the claim as containing an additional limitation, i.e. the cause of the defect, which is not present in the claim. Applicants contend that these remarks obviate the above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection of claims 1, 3-6, 15-16, 18-22 concerning the term "improve"

The Examiner rejected claims 1, 3-6, 15-16, 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the recitation of "improving" throughout the claims is vague and indefinite. The Examiner stated that it is not clear by what criteria this improvement is judged (e.g. amount of training required to create long term memory; duration of a long-term memory; clarity of a long-term memory; or other).

In response, applicants respectfully traverse the Examiner's rejection. Applicants contend that the metes and bounds of the claim are established. Applicants respectfully point the

Examiner's attention to page 20, lines 1-5 of the originally filed specification which states in pertinent part "...for improvement of memory formulation." Applicants contend that based on this, the criteria by which the improvement is judged is adequately defined. The criteria is that "memory formulation" is improved.

Applicants also point out that memory improvement can be tested in numerous ways. One skilled in the art would know how to test for memory improvement. For example, in an animal model, mazes can be used to test the memory improvement in mice. The memory improvement in a human subject can be tested by asking the subject questions based on what they have read. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 3-6, 15-16, 18-22 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and maintained the rejection for the reasons set forth in Paper No. 10 filed 11/10/97.

The Examiner stated that applicant's arguments filed 5/14/98 (Paper No. 11) have been fully considered but are not persuasive. The Examiner stated that applicant argues/alleges on pages 13-15 that (a) the specification allegedly comprises working examples though applicant does not point to such Examples (b) not all actual embodiments need be disclosed (c) the factors which must be considered under MPEP 2164.01 as satisfied (d) complex experimentation is not necessarily "undue" experimentation (e) disclosed experiments that "show the cAMP-responsive gene

expression correlates to memory function" (page 14 of Paper No(s). 11) enable the claims (f) applicant cites in re Brana in the context of human trials and MPEP 2107.02 for "reasonable correlation" (in vitro- in vivo; activity-asserted utility; human trials) to support utility of the claimed invention.

The Examiner stated that in response: (a) the claims are drawn to methods of improving long term memory and in subjects with either a low cAMP responsive gene expression (independent claim 1) or a memory defect (independent claim 15). The Examiner stated that as set forth in the previous Office action, the skilled artisan distinguishes long term potentiation in Aplysia from complex memory processes in primates, further, long term potentiation as a model for memory process in Aplysia itself has been critiqued. The Examiner stated that therefore, the art teaches that long term facilitation is to equivalent to long term memory. The Examiner stated that other aspects of the claims, such as improvement of long term memory in particular subject populations (defined by low cAMP responsive gene expression, general or specific memory defect) are not addressed in the working examples.

The Examiner stated that further, (b-e) though it is agreed that all actual embodiments need not be disclosed and complex under MPEP 2164.01 (see also in re Wands) in regard to the instant invention is not satisfied. The Examiner stated that for examples, the working example(s) are not drawn to the claimed subject matter (also see (e) above, the working examples may show that particular cAMP-responsive gene expression correlates to long term facilitation, however, this is not what is claimed), the nature of the invention is highly complex, the breadth of the claims is extensive and encompasses specific human conditions of different etiologies, and the art points to unpredictability (e.g. see Paper No(s). 10). The Examiner stated that in contrast to applicant's assertion on page 14 that the quantity of

experimentation would not be great human conditions of different etiologies, and the art points to unpredictability (e.g. see Paper No(s). 10). The Examiner stated that in contrast to applicant's assertion on page 14 that the quantity of experimentation would not be great because allegedly the exchange of particulars of the examples for other embodiments is allegedly "routine", for the reasons set forth above and in Paper No(s). 10, one of skill would have reason to doubt the correlation between disclosed examples and the claimed invention, and therefore the experimentation would require creative input and success would be highly unpredictable.

The Examiner stated that applicant's citation of in re Brana and MPEP 2107.02 are not on point because the method claims are rejected for lack of enablement, not utility. The Examiner stated that however, the Examiner notes that human trials are not called for, and importantly the correlation between what is disclosed and what is claims is not unpredictable for the reasons above and in Paper No(s) 10.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that long term potentiation in Aplysia is analogous to and an accepted model of long term memory processes in other mammals. Applicants contend that similar gene structures between Aplysia and mammals suggest that their memory processes are similar. Applicants respectfully point the Examiner's attention to page 24 of the specification which teaches that there is a 21% sequence homology between Aplysia CREB2, mouse ATF-4 and human CREB2. Furthermore, in the bZIP domain, there is 50% sequence homology. This sequence conservation would suggest similar functionality across species and possibly in memory processes. Applicants point out that like its human homolog CREB2, Aplysia CREB2 is a repressor of transcriptional activator CREB1.

Furthermore, applicants respectfully point the Examiner's attention to the paper entitled "CREB1 Encodes a Nuclear Activator, a Repressor, and a Cytoplasmic Modulator that Form a Regulatory Unit Critical for Long Term Facilitation," Cell, vol 95: 211-223 (1998), a copy of which is attached hereto as **Exhibit A**. The reference teaches on page 220 that there is increasing evidence that the transcriptional activator CREB is important for long term synaptic plasticity and long term memory formation is Aplysia, Drosophila and mice. The reference teaches that the Aplysia CREB1 gene is homologous to mammalian CREB. Page 221 teaches that the Aplysia CREB1b polypeptide resembles the mammalian ICER and ICREB repressors both structurally and functionally. Applicants contend that this data tends to support the idea that Aplysia can be used as a model for memory formation in mammals.

Furthermore, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove added new claim 28. Applicants contend that these remarks and the above amendment obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. §102

The Examiner rejected claims 1, 3-5, and 18-21 under 35 U.S.C. §102(a or b) as being anticipated by Yin is maintained, for the reasons set forth in Paper No(s). 10 filed 11/10/97.

The Examiner stated that applicant's arguments filed 5/14/98 (Paper No. 11) have been fully considered but are not persuasive. The Examiner stated that applicant argues on page 18 that: (a) over expression of dCREB-2a reduces the number of training trials needed to establish long term memory (b) that the Examiner asserts without support that dCREB-2a interferes with CRE binding (c) that Yin does not teach a method wherein in the subject

population which has decreased cAMP responsive gene expression due to binding of CREBP2 to a protein or DNA required for this binding.

The Examiner stated that in response: (a) reduction training needed to establish long term memory reads upon improved long term memory. (b) CREBP (CRE binding protein) by definition binds CRE. The Examiner stated that claims 1 and 15 use "capable of" language, dCREB-2a is capable of binding CRE. The Examiner stated that therefore, the single method step of the claim is fulfilled. The Examiner stated that additionally, the final outcome of the claim, improved memory, is disclosed. The Examiner stated that though the authors admit the exact mechanism of action is not known, one of skill in the art would expect that the modulation of cAMP gene expression is an inherent property of the method, because of CRE's role in this expression, and as above, Yin et al anticipate all the method steps of the instant claims. The Examiner stated that © the claim no longer recite this limitation.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that Yin does not anticipate the claimed invention. Claim 1 recites:

> A method to improve long-term memory in a subject whose cAMP-responsive gene expression is decreased which comprises administering to the subject a compound capable of inhibiting binding of a cAMP-responsive-element-binding-protein-2 to a transcription factor protein or to a DNA required for cAMP-responsive gene expression in an amount effective to increase cAMP-responsive gene expression in the subject and thereby improve the subject's long term memory.

Applicants respectfully remind the Examiner that to anticipate a claim, the reference must teach every element of the claim. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. See MPEP 2131.

Applicants point out that the claim recites a method to improve long-term memory in a subject whose cAMP-responsive gene expression is decreased. Applicants contend that Yin does not teach every element of the claim. Yin teaches that induced expression if a dCREB2 activator isoform enhances long-term memory in Drosophila. Applicants contend that there is no disclosure in Yin of a method to improve long-term memory in a subject. Yin, at most, is merely a study of the induced expression of the dCREB2-a activator isoform in transgenic flies.

Furthermore, applicants respectfully point out that the prior art refers to dCREB2a and dCREB2b. Applicants contend that the isoforms cited in the Yin reference are related to Drosophila CREB1. Applicants believe that although the name "CREB2" appears in the Yin reference, it does not appear to relate to the CREB2 described in the subject application and thus, would not in any way predict it's function. Accordingly, applicants respectfully contend that the Yin reference does not teach one skilled in the art that inhibiting the binding of the CREB2 defined in the subject claims will increase cAMP gene expression. Therefore Yin et al should be removed as a reference against the claimed invention. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

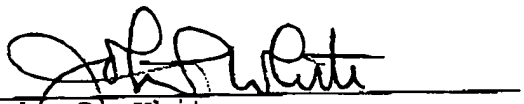
Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of objection and rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the $435.00 fee for a three-month extension of time and $9.00 fee for additional claims is deemed necessary in connection with the filing of this Amendment and authorization is hereby given to charge this amount to Deposit Account No. 03-3125. If any additional fee is deemed necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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